species can come together within a broadly defined niche.

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Division of Organisms and Environment, University of California, Berkeley CA94720-3114, USA.
E-mail: gillespie@berkeley.edu

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Quality Control: Putting Protein Aggregates in a Bind

Asymmetric inheritance of protein aggregates in budding yeast is a fascinating yet controversial area of aging research. A recent study demonstrates that unfolded protein aggregates are confined to the mother by tethering to organelles rather than retrograde transport.

Jay R. Unruh[1], Brian D. Slaughter[1], and Rong Li[1,2,*]

One of the most intriguing aspects of aging is the ability of cells to asymmetrically distribute potentially harmful protein aggregates during the process of cell division and therefore allow half of the progeny of each division to begin life with a clean slate. Recent studies have investigated the mechanism for this phenomenon in budding yeast [1,2], which undergoes asymmetric mitotic cell division and segregation of aging related aggregates between the mother (aged) and bud (newborn) [3,4]. A debate has centered over the role of the motility of protein aggregates and the contribution of actin in generating asymmetric inheritance. A new study by Spokoini *et al.* [5] now reveals that certain aggregates are asymmetrically inherited due to confinement of their motility as a result of accumulation in juxtanuclear quality control compartments (JUNQ) or insoluble protein deposit compartments (IPOD).

An earlier study suggested that an active transport mechanism involving actin cables is responsible for the clearance of heat-shock-induced protein aggregates, decorated with the Hsp104 chaperone, from the bud to the mother prior to cytokinesis (Figure 1A, top) [1]. This hypothesis was supported by data showing that disruption of the actin network led to defects in asymmetric inheritance of aggregates and that some aggregates in the bud moved across the bud neck into the mother side. A later study from our laboratory [2] questioned this hypothesis, firstly on the grounds that cell polarity and well oriented actin cables only exist in a limited time window prior to entry into mitosis, well before cell division [6]. It then used quantitative particle tracking analysis of hundreds of protein aggregates to show that aggregates move in a stochastic but confined manner that does not contain any statistically significantly transport component throughout the cell cycle [2] (Figure 1A, middle). This finding led to a mathematical model to explain asymmetric aggregate inheritance based on the study's phenomenological measurements. The model predicted that the observed properties of the confined diffusion of the aggregates combined with the geometry of budding yeast cells were sufficient to yield a very low probability of aggregates entering the bud from the mother during the time span of a cell cycle. Parameters of this model that impact this probability include the cell-cycle duration, the width of the opening between the bud and the mother, the presence or absence of confinement, and the diffusion coefficient of the aggregates.

The above model (referred to herein as 'the stochastic model'), however, was based simply on the experimentally measured diffusion parameters and made no assumptions about the mechanism underlying the observed confined diffusion of the

Hsp104-decorated aggregates. The new study by Spokoini *et al.* [5] now sheds further light on the cellular basis of the confined diffusion of protein aggregates and demonstrates its importance in the asymmetric inheritance of misfolded proteins. The authors presented evidence that misfolded proteins form short-term stress foci that can be processed through the ubiquitination pathway and accumulate in the JUNQ or form an IPOD [7] neighboring the vacuole. The motion of these stress foci is confined to the surfaces of organelles (the nucleus in the case of JUNQ, and the vacuole for IPOD) in the mother cell (Figure 1A, bottom). To provide evidence that organelle confinement is important for the asymmetric inheritance of damaged proteins, the authors examined the aggregation-prone protein Ubc9^{ts} in an *hsp104* deletion strain, where stress foci are prevalent and not restricted to IPOD or JUNQ [5]. The authors observed that under this condition there was a high percentage of cells with one or a few aggregates inherited by the bud [5].

The new observations summarized above provide experimental validation of several predictions that can be made from the stochastic model proposed earlier. First, the stochastic model indeed predicted that a lack of confinement in aggregate diffusion increases the chance of aggregates moving across the bud neck and being inherited by the bud [2], although even under this scenario the actual distribution of the aggregates remains asymmetric, consistent with the qualitative impression of the results shown in Spokoini *et al.* (Figure 2 in [5]). Second, an increase in the concentration of aggregates in the mother cells due to the lack of Hsp104 chaperone activity, as shown in this and the previous studies [1,2], also predicts an increased probability of aggregate inheritance by the bud (Figure 1B, top). Third, given that the length of the cell cycle after heat shock in the *hsp104Δ* mutant is longer than a normal yeast cell cycle (~ 180 min, Figure 2B in Spokoini *et al.* [5], vs ~90 min used in the simulations in [2]), the stochastic model indeed predicts a reduced probability of having the bud fully clear of aggregates at the end of a cell cycle (Figure 1B, bottom). As such, the observed spillage of aggregates into the bud in *hsp104Δ*

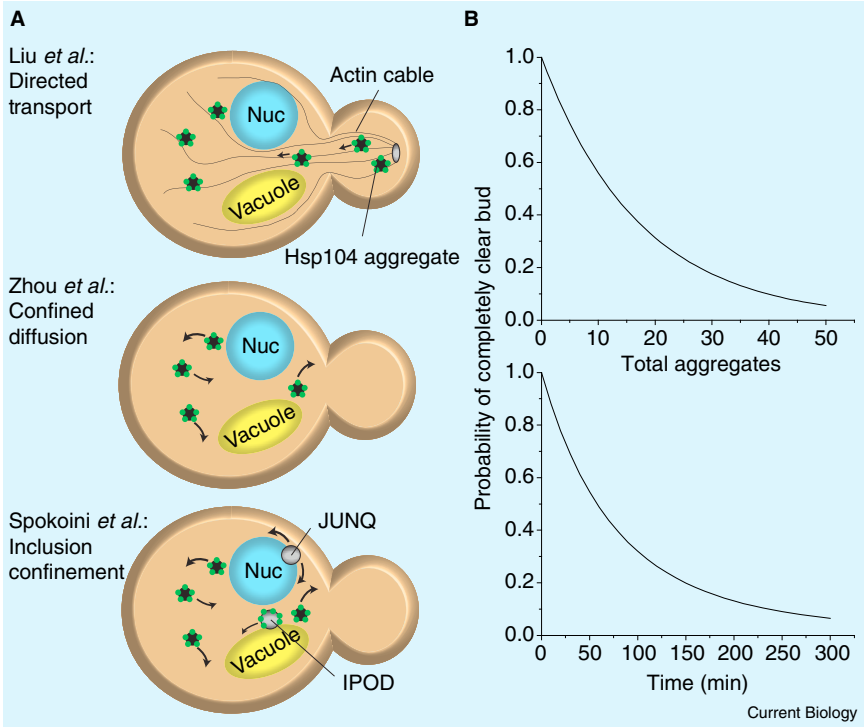

Figure 1. Models for asymmetric inheritance of protein aggregates in budding yeast.

(A) Schematic illustration of the different proposed models of protein aggregate motility in budding yeast. Top: The model in which protein aggregates undergo retrograde transport from the bud to the mother along actin cables [1]. Middle: Protein aggregates undergo confined diffusion [2]. The slow diffusion rate, the presence of confinement and the geometry of bud neck predict their preferential detainment in the mother. Bottom: Confinement of protein aggregate motion through association with JUNQ and IPOD on the surface of the nucleus and vacuole, respectively [5]. (B) Simulations of the stochastic model examining the change in the probability of having buds completely clear of protein aggregates as a function of the initial number of aggregates in the mother (top) and cell-cycle time span (bottom). Methods of the modeling are described in detail in [2]. The top graph used a cell cycle time of 90 minutes; the bottom graph is an example using 20 total aggregates.

cells can be qualitatively explained based on the stochastic model. It is interesting to note that the protein aggregates observed in the previous studies [1,2] were far greater in number than just the singular IPOD and JUNQ stress aggregates described in Spokoini *et al.* [5], yet their motion was clearly confined [2]. This raises a question regarding whether additional confinement mechanisms exist to constrain the movement of the protein aggregates outside of IPOD and JUNQ.

One point of contention of the studies discussed above is the role of actin in asymmetric inheritance of heat-shock-induced 'stress foci'. Liu *et al.* [1] proposed, based on some presented examples of aggregates moving from the bud to the mother, that retrograde transport along actin cables away from the bud was responsible for asymmetric aggregate inheritance. Contrary to this model, our work [2] found neither a directional bias in aggregate motion between the mother and the bud nor any reduction in cells with buds fully clear of aggregates after deletion of genes encoding the formin proteins responsible for the nucleation of actin cables. Although Spokoini *et al.* [5] do not directly address the role of actin, the qualitative model based on confinement to the surface of mother-based organelles also precludes the need for retrograde transport via actin. Although actin does not appear to play a role in aggregate segregation through the polarized, actin-cable-based transport system, actin does seem to influence aggregate mobility in the cytoplasm, given that, in the presence of latrunculin A, an actin polymerization inhibitor, the diffusion of aggregates was drastically reduced [2]. An intriguing possibility to be explored in the future is that random motion of aggregates powered by finer actin structures not previously

characterized in yeast might facilitate the capture by or consolidation of protein aggregates into quality control compartments. In conclusion, recent data in yeast are converging on the notion that confinement as opposed to active transport is the primary mechanism to restrict damaged proteins to the altruistic mother, providing a means of quality control for maintaining the vitality of the population.

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[1]Stowers Institute for Medical Research, 1000 East 50th Street, Kansas City, MO 64110, USA. [2]Department of Molecular and Integrative Physiology, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160, USA.
*E-mail: rli@stowers.org

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Immune Priming: Mothering Males Modulate Immunity

The transfer of immunity from mother to offspring is widespread in animals. The father's contribution to this is usually negligible. However, in a sex-role reversed pipefish where fathers do the mothering, fathers make an important immune priming contribution, too.

M. Cristina Keightley[1], Bob B.M. Wong[2], and Graham J. Lieschke[1,*]

Non-genetic transfer of immunity from mother to offspring is a well-recognized phenomenon known as transgenerational immune priming. Mammals, for instance, exchange immunological information on abundance and composition of pathogens to offspring via the placenta and antibody-rich mother's milk [1], while in fish and insects, mothers are known to make immunological contributions through their eggs [2,3]. Transgenerational defense transfer even occurs in plants [4]. What evolutionary selection pressure is at play here? The paradigm is that offspring who are destined to be raised in a similar disease environment to their mothers will benefit from a maternal enhancement of offspring immunity that reflects the current environmental challenges. The context is a co-evolutionary 'arms-race' between microorganisms and their hosts. As microorganisms evolve stronger virulence, this simultaneously exerts strong evolutionary pressure on hosts to increase their resistance phenotype and genotype [5].

Since it is the female that typically invests time and physical resources in gestating and rearing the young, the investment of transgenerational immunity is both determined and constrained by the maternal immune response. Traditionally, the paternal contribution to immune priming was thought to be negligible. This is because male gametes are considered too small to carry a cargo of immune-modulating proteins such as antibodies [6] and males cannot be guaranteed to share the host–pathogen environment of the offspring.

But what if males were to invest more in nurturing offspring? Would a substantially increased male contribution of physiological resources towards his offspring be accompanied by an augmented male contribution to offspring immune priming? To address these questions experimentally, a model that dissociates the almost invariable link between female gender and high reproductive investment is required.

In contrast to most vertebrate groups where male parental care is rare [7], in fish species that actually look after their offspring, care by males is more often the rule rather than the exception. Selection pressures driving this behaviour may be the greater certainty of paternity it affords, and the ability of males to care for multiple broods simultaneously without impinging on additional mating opportunities [8]. Of those species with exclusively male parental care, few can match the extreme specialization for looking after offspring seen in the Syngnathids — the group comprising the seadragons, pipefishes and iconic seahorses. In syngnathid fishes, females transfer their yolk-rich eggs to the male during mating, who then take exclusive care of the offspring by osmoregulating and nourishing the developing embryos in remarkably specialized structures located on the male's abdomen or tail [9,10]. The diversity of brooding structures varies among syngnathids, from simple gluing of the eggs to the male's belly through to the sophisticated brood pouches seen in seahorses and some pipefish species [9,10]. Typical of the extreme specialization for parental care seen in this group, the male broad-nosed pipefish *Syngnathus typhle* (Figure 1A) has a placenta-like structure within its brood pouch (Figure 1B) [11,12]. This led Roth *et al.* [13], as reported in a recent issue of *The American Naturalist*, to hypothesize that male pregnancy in *S. typhle* may provide a mechanism for males to selectively contribute to offspring immunity in a manner reflecting the paternal immune experience, and furthermore, that this would be at the expense of maternal contribution to immune priming.

To simulate a pathogenic environment, parental pipefish were exposed to a mix of several phylotypes of heat-killed *Vibrio* bacteria. Immune